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BLADDER CANCER IN PET DOGS: A SENTINEL FOR ENVIRONMENTAL CANCER?

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Hayes, H. M., Jr. (Environmental Epidemiology Branch, NCI, Bethesda, MD 20205), R. Hoover, and R. E. Tarone. Bladder cancer in pet dogs: A sentinel for environmental cancer? *Am J Epidemiol* 1981;114:229-33.

Proportional morbidity ratios (PMRs) were calculated for cancers, by site or type, in 8760 pet dogs seen at 13 veterinary medical teaching hospitals in the United States and Canada. A significant positive correlation was seen between the PMRs for canine bladder cancer and the overall level of industrial activity in the host county of the hospital. An analysis of mortality from bladder cancer among white men and women in the same US counties showed similar correlations with industrial activity. Canine bladder cancer could be a sentinel condition whose investigation in certain locales might lead to early identification of carcinogenic hazards in the general environment.

bladder neoplasms; carcinogens, environmental; dogs; environmental pollutants; industry

In the search for the determinants of human cancer, the role of environmental pollutants remains to be clarified. For instance, the influence of air pollution on human lung cancer is difficult to distinguish from the more potent effects of tobacco smoking and certain occupational exposures (1).

Laboratory animals have been used to evaluate the potential hazards of industrial pollutants. However, this approach is encumbered by time and cost constraints with limited generalizability to the larger experience in the outside environment. The continuing health experience of pet animals may provide new leads in the evaluation of environmental hazards since they share with their owners many of the exposures to environmental pollutants. The most common pet animal, the dog, has often provided an excellent model for the study of human neoplasia (2).

To assess possible relationships between canine cancer and industrial activity, a study was made of the proportional morbidity ratios of various types of cancer among pet dogs diagnosed at veterinary medical teaching hospitals. These proportional morbidity ratios were correlated with an estimate of industrial activity in the geographic area surrounding the hospitals. In this manner we sought to determine if general industrialization was related to the prevalence of specific cancers in dogs. If so, certain tumors of the pet dog might serve as prognostic sentinels for environmentally induced cancers in man.

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The following veterinary universities provided the data: Colorado State, Iowa State, Kansas State, Michigan State, Ohio State, Purdue, California, Georgia, Illinois, Minnesota, Missouri, Guelph, and Saskatchewan.

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Materials and methods

We obtained abstracts of medical records for all pet dogs seen at 13 North American veterinary medical teaching hospitals. Each abstract contains 1) descriptive data about the dog (including clinic, a unique sequentially assigned patient number, age, sex, and gonadal status), 2) diagnoses, and 3) various laboratory and other procedures used to confirm diagnoses (3). Abstracts representing approximately 1.1 million clinical events covering an average of 9.5 consecutive years of medical activity ending June 1978 were reviewed.

Dogs with one or more microscopically confirmed primary cancers were identified and tabulated according to site of origin, reporting facility, age, and sex of the dog. Cases having two or more organ sites involving different primary cancers were counted once in each appropriate group. Dogs with multiple malignancies which involved only one organ site were counted once in the tabulation.

Our survey identified 9460 malignancies (from 8760 individual dogs) qualifying for inclusion in one of the cancer groups; dogs with only nonmelanoma skin cancer were excluded. Cancer cases were grouped as follows: oral, nasal, bladder, lung, breast, hemolymphopoietic, bone and joint, genital, gastrointestinal, and miscellaneous. Oral, nasal, lung, and bladder categories reflect the sites of entry and elimination of general environmental carcinogens. These have been the sites where the effects of environmental carcinogens have been most conspicuous in man (4). The other sites represent comparison groupings where canine cancer frequently occurs and for which we have no a priori suspicion of a relationship to pollutants in the general environment.

The overall industrial activity in each of the 11 US counties surveyed with veterinary facilities was estimated by the percentage of men ≥16 years of age employed in manufacturing according to the 1970 US Census (5). Similar percentages were calculated for the locations of the two Canadian hospitals; these percentages were based on men ≥15 years of age tabulated in the 1971 Canadian Census (6). The percentage values ranged from 5.2 to 32.4 (table 1).

A proportional morbidity ratio for each cancer group was calculated for each medical facility (n = 13) with adjustment for age and sex differences between facilities. For each age/sex category, the ratio of the number of cancer cases of a specific type in "all hospitals combined" to the total number of all cancer cases in "all hospi-

Table 1

Percentage of men employed in manufacturing in study counties with veterinary medical teaching hospitals

Veterinary medical teaching hospital	County, state	%
University of Minnesota	Ramsey, MN	32.4
Michigan State University	Ingham, MI	29.8
Ohio State University	Franklin, OH	27.9
Purdue University	Tippecanoe, IN	23.4
Colorado State University	Larimer, CO	17.1
University of Georgia	Clarke, GA	15.4
University of Guelph	Wellington, ON, Canada	13.8
University of California	Yolo, CA	10.9
University of Illinois	Champaign, IL	10.5
University of Missouri	Boone, MO	7.8
Iowa State University	Story, IA	6.9
University of Saskatchewan	Div. 11, SS, Canada	5.3
Kansas State University	Riley, KS	5.2

tals combined" was used as a standardized odds ratio. An expected number of cancers for the specific site/type in each age/sex category at a given facility was obtained by multiplying each standardized odds ratio by the total number of cancer cases in the corresponding age/sex category at the facility. The expected numbers were summed for each facility to derive a total number of each cancer type that would be "expected" if the age- and sex-specific proportional distribution of cancers diagnosed in "all hospitals combined" prevailed. The ratio of the observed-to-expected number of cases was used as the estimate (proportional morbidity ratio) of canine risk for each cancer type at each facility relative to that in "all of the hospitals combined." Correlation coefficients (r) (7) were used to measure the association between these proportional morbidity ratios and the estimate of industrial activity.

Results

Correlation coefficient values for the proportional morbidity ratio of each cancer group with industrial activity are shown in table 2. Increasingly positive associations were found for oral, nasal, bone and joint, and bladder cancers; the latter was statistically significant, $p < 0.05$.

It has been surmised that veterinary teaching hospitals often see referral patients that come from outside the clinic's regular practice area and these patients are no more likely to be referred for one type of cancer than another. If untrue, these referrals could greatly influence our findings. To assess this possibility, a sample of permanent medical record files of US veterinary medical teaching hospitals were reviewed to identify patients living within a 25 mile (40 km) radius of the teaching hospital.

Our sample for review was composed of all bladder cancer patients and all other cancer cases diagnosed after 1969 for patient numbers ending in 0, 1, 2, 4, 5, 7, and 9; the sum was 4880 dogs. The postal zip code for each pet owner's home was abstracted and matched against postal zip codes designating the area within a 25 mile radius of that hospital (8). Surprisingly, 64 per cent of these cases lived outside the designated practice area.

Age- and sex-adjusted proportional morbidity ratios were recalculated for bladder and bone and joint cancers for each medical facility with the 1771 cases in our sample that lived in proximity of their treatment facility. The recalculated correlation coefficient for bladder cancer rose to 0.75 (p = 0.008, df = 9) (figure 1), whereas it declined somewhat for bone and joint cancers (r = 0.50, p > 0.11, df = 9).

The 25 mile practice radius encompassed portions of other counties in addition to the county site of the hospital. Further analysis was undertaken to eval-

TABLE 2

Number of canine cancers by site/type and correlation coefficients (r) for the association of site/type-specific proportional morbidity ratio and the industrial activity in the geographic area studied

Cancer group	No. of cases	r	p
Bladder and lower urinary tract	209	0.59	0.03
Bone and joint	1045	0.54	0.06
Nasal	444	0.44	0.13
Oral	819	0.40	0.17
Gastrointestinal	284	0.32	0.29
Lung	260	0.20	0.51
Hemolymphopoietic	2423	0.14	0.64
Miscellaneous	2265	−0.41	0.17
Genital	442	−0.62	0.02
Breast	1269	−0.66	0.02

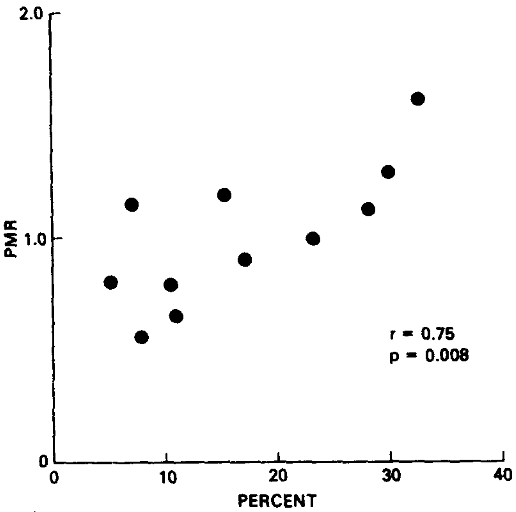

FIGURE 1. Proportional morbidity ratios (PMRs) of bladder cancer among dogs living in a 25 mile (40 km) radius of their treating medical facility. PMRs plotted according to the percentage of men employed in manufacturing in the US county with the medical facility. r = correlation coefficient.

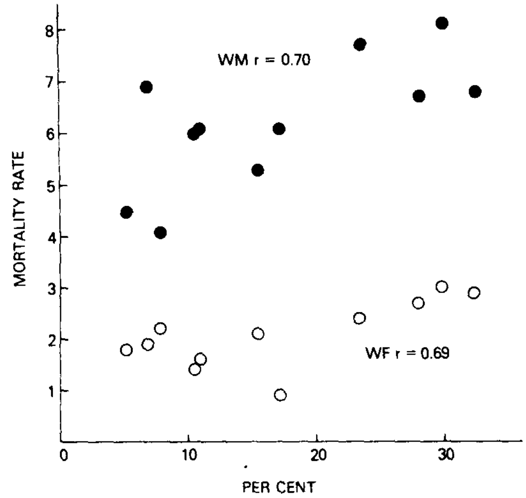

FIGURE 2. Age-adjusted mortality rate per 100,000 population for bladder cancer (ICD 181) in white men and women living in US counties with surveyed veterinary teaching hospitals. Rates plotted according to the percentage of men employed in manufacturing in 1970. r = correlation coefficient.

uate the effect on the correlation coefficient for bladder cancer using a new measure of industrial activity. This was based on the weighted proportion of men employed in manufacturing using the percentage of area of each county included within the 25 mile practice radius. Reanalysis with the 1771 cases showed the correlation coefficient value for canine bladder cancer to be about the same (r = 0.80, p = 0.003, df = 9).

To characterize the human experience, we tabulated the age-adjusted mortality rates, 1950–1969 (9), for cancer of the bladder (*International Classification of Diseases* (ICD) code 181) among white men and women in each US county with a veterinary medical teaching hospital in our survey and correlated these rates with industrial activity (data were not available for the Canadian counties). The correlation coefficient values were 0.70 for men and 0.69 for women ($p < 0.02$, df = 9) (figure 2).

DISCUSSION

Our analysis of veterinary data revealed that of the four sites of cancer under a priori suspicion, three (oral, nasal, and bladder) showed some evidence of correlation with the presence of manufacturing industries. Of these three, only bladder cancer showed a strong and statistically significant association. Lung cancer, another site under suspicion, showed little correlation with industrial activity (r = 0.2). This may be explained by the capacity of the dog's mouth and nose to effectively filter inhaled particulate matter as noted in other animals (10).

One comparison site grouping, bone and joint cancers, showed a relatively strong correlation, a finding partially explained by referral bias. All of the other cancer sites chosen for comparison purposes showed either a negative or no correlation. It should be noted that when using a proportional measure of effect (e.g., proportional morbidity ratio), any strong positive association will force some associations to be negative as all of the individual proportional morbidity ratios must sum to 1.0 for the total. Also, a breed susceptibility for bladder cancer has been reported for the Scottish terrier, Shetland sheepdog, beagle, and collie (11). We did not control for breed in these determinations because of the small number of cases available in each stratum when characterized by hospital, age, and sex.

The findings of this study suggest that the bladder cancer experience of pet dogs resembles that of human beings living in the same general locale. A dose-response relationship is suggested with the higher rates of manufacturing (figure 1). Yet, the lower exposure categories are irregular, arguing against this causal relationship. In this particular analysis, it seems reasonable that the irregularity could result from the uncertainties created by the small number of cases participating in each proportional morbidity ratio in the lower exposure areas.

The geographic correlations of human bladder cancer with industrial activity could be due to factors related to industrialization other than environmental pollution, specifically smoking habits or occupation exposures (12). In addition, the strength of correlation with industrial activity and human bladder cancer was similar in men and women, suggesting that factors other than occupational ones were also responsible. A dose-response relationship is particularly evident in the mortality rates for women with manufacturing activity (figure 2), which we do not believe can be attributed to occupational exposure to chemical carcinogens.

The correlation seen with canine bladder cancer would not be attributed to the confounding or interactive effects of tobacco or occupational exposures. It is possible, therefore, that the correlations in this study, particularly in pet dogs and in women, relate to industrial carcinogens that have escaped into the general environment, although the specific agents remain to be identified.

Forty years ago Hueper et al. (13) demonstrated that the dog reacts to chemical carcinogens of the bladder in a similar manner to man. The latent period in man, however, is estimated to be at least 20 years after first exposure (14), compared to no more than 10 in the pet dog (11). Use of the pet dog as a sentinel could lead to early identification of carcinogenic hazards in the general environment.

References

1. Fraumeni JF Jr, ed. Persons at high risk of cancer. New York: Academic Press, 1975;131-290.
2. Hayes HM Jr. The comparative epidemiology of selected neoplasms between dogs, cats, and humans. A review. Eur J Cancer 1978;14:1299-1308.
3. Tjalma RA, Priester WA, Adelstein EH, et al. Clinical records systems and data retrieval function in veterinary medicine: a proposal for systematic data programming. J Am Vet Med Assoc 1964;145:1189-97.
4. Cole P. Lower urinary tract. In: Schottenfeld D, ed. Cancer epidemiology and prevention. Springfield: Thomas, 1975;233-62.
5. US Bureau of the Census. US Census of Population: 1970, Vol. 1. Characteristics of the population. Washington DC: US GPO, 1973.
6. Statistics Canada. 1971 Census of Canada. Occupations. Revised, catalogue nos. 94-718/720. Ottawa, 1974.
7. Snedecor GW, Cochran WG. Statistical methods. 6th ed. Ames: Iowa State University Press, 1968;172-98.
8. US Department of Commerce. Codes for named populated places and related entities of the states of the United States. FIPS 55, Vol. 1 & 2. Springfield VA: US GPO, 1978.
9. Mason TJ, McKay FW. U.S. cancer mortality by county: 1950-1969. Washington DC, US GPO, 1973.
10. Nettesheim P, Schreiber H. Handbuch der Allgemeiner Pathologie. Berlin: Springer Verlag, 1975;604.
11. Hayes HM Jr. Canine bladder cancer: epidemiologic features. Am J Epidemiol 1976;104:673-7.
12. Blot WJ, Fraumeni JF Jr. Geographic patterns of bladder cancer in the United States. JNCI 1978;61:1017-23.
13. Hueper WC, Wiley FH, Wolfe HD. Experimental production of bladder tumors in dogs by administration of beta-naphthylamine. Journal of Industrial Hygiene and Toxicology 1938; 20:46-84.
14. Hoover R, Cole P. Temporal aspects of occupational bladder carcinogenesis. N Engl J Med 1973; 288:1040-3.